TIER 1 SCREENING SIDS DOSSIER ON THE HPV PHASE ..... CHEMICAL

CYCLOHEXANONE OXIME

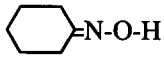
CAS No. 100-64-1

First Draft
March 1, 2006

CONTENTS

SIDS PROFILE

DATE: November 30, 2005

1.01 A.	**CAS No.**	108-93-0
1.01 C.	**CHEMICAL NAME**	CYCLOHEXANONE OXIME
1.01 D.	**CAS DESCRIPTOR**	Not applicable
1.01 G.	**FORMULA & STRUCTURE**	$C_6H_{12}0$ 
1.5	**QUANTITY**	No current production information available
1.7	**USE PATTERN**	Primarily used in a closed process system in the synthesis of caprolactam which, in turn, is used to produce polycaprolactam (Nylon-6) fibers and resins.
1.9	**SOURCES AND LEVELS OF EXPOSURE**	Process leaks during manufacture of caprolactam
TEST PLAN JUSTIFICATION /ISSUES FOR DISCUSSION	No additional testing was recommended for "Environmental Fate and Pathways", "Ecotoxicity", and "Reproductive Toxicity" categories based on "closed system intermediate" status for cyclohexanone oxime (and low occupational and environmental exposure potential) (See APPENDIX (pp. 18-30)in HPV Test Plan document. Adequate studies were available to meet HPV requirements for "Physical/Chemical Properties", "Acute Toxicity"and "Repeated Dose Toxicity" categories. However, a developmental toxicity study in rats by the oral route will be conducted to satisfy HPV requirements for the "Reproductive/Developmental Toxicity" category.	

Tier 1

SIDS SUMMARY

DATE: March 1, 2006

CAS NO: 100-64-1		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N			Y	N
2.2	Boiling Point	Y	N	N			Y	N
2.3	Density	Y	N	N			Y	N
2.4	Vapour Pressure	Y	N	N			Y	N
2.5	Partition Coefficient	Y	N	N			Y	N
2.6	a. Water Solubility	Y	N	N			Y	N
	b. pH and pKa values							
2.7	Flash Point	Y	N	N			Y	N
2.8	Flammability	Y	N	N			Y	N
2.12	Oxidation: Reduction Potential	N						N
2.13	Adsorption/Desorption to Soil	N						N
ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	Y	N	N		Y	N	N*
3.1.2	Stability in water	Y	N	N		N	N	N*
3.3	Transport and Distribution	N						N*
3.5	Biodegradation	N						N*
ECOTOXICITY								
4.1	Acute toxicity to Fish	Y	N	N			Y	N*
4.2	Acute toxicity to Daphnia	N						N*
4.3	Toxicity to Algae[1]	N						N*
TOXICITY								
5.1	Acute Toxicity:							
5.1.1	Acute Oral	Y	N	N			Y	N
5.1.2	Acute Inhalation	N		N				N
5.1.3	Acute Dermal	Y	N	Y			Y	N
5.1.4	Acute intraperitoneal	Y	N	N			Y	N
5.4	Repeated Dose (General)	Y	N	Y			Y	N
5.5	Genetic Toxicity *in vitro*							
	. Gene mutation	Y	N	Y			Y	N
	. Chromosomal aberration	Y	N	Y			Y	N
5.6	Genetic Toxicity *in vivo*	Y	N	Y			Y	N
5.7	Reproduction Toxicity	N						N*
5.8	Developmental Toxicity/Teratogenicity	N						Y

*Decision based on a claim for "closed system intermediate" status for cyclohexanol oxime based on low occupational exposure potential and negligible environmental release potential; the result of such a status is reduced SIDS testing for this oxime (See APPENDIX (pp. 18-30) of HPV Test Plan document).

1. GENERAL INFORMATION

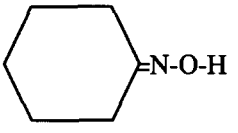
1.01 SUBSTANCE INFORMATION

A. CAS-Number 100-64-1

C. OECD Name Cyclohexanone oxime

D. CAS Descriptor Not applicable

G. Structural Formula $C_6H_{11}NO$



1.5 QUANTITY

Remarks: Cyclohexanone oxime is primarily consumed in a closed system during the production of caprolactam.

1.7 USE PATTERN

Remarks: Most of the cyclohexanone oxime produced is used in the production of caprolactam during the manufacture of Nylon-6 polymer.

1.9 SOURCES OF EXPOSURE

Process leaks during manufacture of caprolactam are remotely possible. However, engineering controls and recommended protective equipment/clothing will assure low exposure potential via inhalation, dermal and eye routes of administration.

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

Value: 190 - 196°F

Decomposition: No Data

Sublimation: No Data

Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	None
Reliability:	[4] Not assignable because limited study information was available.
Reference:	DSM Chemicals North America, Inc. Material Safety Data Sheet: Cyclohexanone Oxime. Julu 31, 1996.

2.2 BOILING POINT

Value:	406°F
Pressure:	Not available
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	No additional data
Reliability:	[4] Not assignable because limited study information was available.
Reference:	DSM Chemicals North America, Inc. Material Safety Data Sheet: Cyclohexanone Oxime. Julu 31, 1996.

2.3 DENSITY

Type:	Bulk density [ ]; Density [ ]; Relative Density [x]
Value:	0.97
Temperature:	Not given
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	No additional data
Reference:	DSM Chemicals North America, Inc. Material Safety Data Sheet: Cyclohexanone Oxime. Julu 31, 1996.

2.4 VAPOR PRESSURE

Value:	0.029 mmHg
Temperature:	77°F
Method:	calculated [ ]; measured [ ]
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	No additional data
Reliability:	[4] Not assignable because limited study information was available.
Reference:	DSM Chemicals North America, Inc. Material Safety Data Sheet: Cyclohexanone Oxime. Julu 31, 1996.

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

$\log_{10}$Pow:	0.84
Temperature:	25°C
Method:	calculated [ ]; measured [X]
Result:	Cyclohexanone oxime log Pow = 0.84
Remarks:	No other information available
Test Substance:	Cyclohexanone oxime (? purity)
GLP:	Yes [ ] No [ ] ? [x]
Reliability:	[4] Not assignable because limited study information was available.
Reference:	TOXNET Search on Cyclohexanone Oxime. ChemID Plus Advanced Search: Physical Properties, September 8, 2005.

2.6 WATER SOLUBILITY

Value:	1.5 wt%
Temperature:	68°F
Description:	[ ]Of very high solubility [ ]Of high solubility [ ]Soluble [X]Slightly soluble [ ]Of very low solubility [ ]Not soluble
Method:	No information

GLP:	Yes [ ] No [ ] ? [X]
Remarks:	No additional data
Reliability:	[4] Not assignable because limited study information was available
Reference:	DSM Chemicals North America, Inc. Material Safety Data Sheet: Cyclohexanone Oxime. Julu 31, 1996.

2.7 FLASH POINT: 181.4°F (SF Closed Cup)

2.8 AUTO FLAMMABILITY: 545°F

2.9 flammability limits: lfl = 1.3%

2.12 OXIDATION:REDUCTION POTENTIAL – No information available

2.13 ADSORPTION/DESORPTION TO SOIL – No information available

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY – No information available

3.1.1 PHOTODEGRADATION

Type:	Air [X]; Water [ ]; Soil [ ]; Other [ ]
Rate constant:	7.07E-12 (cm^3/molecules-sec)
Method:	Calculated (method unknown)
Remarks:	No additional information was available.
Reliability:	[4] Not assignable because limited study information was available
Reference:	TOXNET Search on Cyclohexanone Oxime. ChemID Plus Advanced Search: Physical Properties, September 8, 2005.

3.1.2 STABILITY IN WATER

Summary:	No specific study to measure hydrolysis in water was found. However, a manufacturer's MSDS states that cyclohexanone oxime is stable in water and undergoes hydrolysis only at sustained temperatures (250 - 300°F).
Reliability (Klimisch Code):	[4] Not assignable because limited study information was available

Reference: DSM Chemicals North America, Inc. Material Safety Data Sheet: Cyclohexanone Oxime. July 31, 1996.

3.2 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAY – No information available

3.5 BIODEGRADATION – No information available

4. ECOTOXICOLOGICAL DATA

4.1 ACUTE TOXICITY TO FISH

A. Preferred Result

Type of Test: static [ ]; semi-static [ ]; flow-through [X]; other [ ]

Species: Fathead Minnow

Exposure Period: 96 Hours

Results: LC_{50} = 208 mg/L (189 mg/L min to 230 mg/L max)

Analytical monitoring: Yes [X] No [ ]

Method: No information available

Test substance: Cyclohexanone oxime (purity unknown)

GLP: Yes [ ] No [X]

Remarks: Reported as "not acutely toxic"

Reliability: [4] Not assignable because limited study information was available

Reference: Geiger, D.L., et al. Acute Toxicity of Organic Chemicals to Fathead Minnows. Volume 5. Center for Lake Superior Environmental Studies, University of Wisconsin – Superior, WI I: 332, 1990.

B. Supporting Data

One other aquatic toxicity reference which has not yet been located is the following: Applegate, V.C. et al. Toxicity of 4346 Chemicals to Larval Lampreys and Fishes. Spec. Sci. Rep. Fish No. 207, Fish Wildlife Service, U.S.D.I., Washington, D.C., 1957.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES – No information available

4.3 ACUTE TOXICITY TO AQUATIC PLANTS (e.g. Algae) – No information available

5. TOXICITY

5.1.1 ACUTE ORAL TOXICITY

A. Preferred Result

Type of Test:	LD
Species:	Rat (species/strain unknown)
Value:	>500 mg/kg
Method:	Unknown
Test substance:	cyclohexanol (? purity)
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	No information – full reference has not yet been located
Reliability:	**[4]** Not assignable because limited study information was available
Reference:	National Academy of Sciences, NRC Chemical-Biological Coordination Center Review 5: 26, 1953

B. Supporting Data:

Type:	LD
Species:	Fischer 344 Rats (5/sex/dose)
Value:	> 300 mg/kg
Method:	Subacute oral gavage study (10 doses at 300 mg/kg bw)
Test substance:	Purity (>99.5%)
GLP:	Yes [X] No [ ] ? [ ]
Remarks:	No compound-related mortality after 10 doses at ≤300 mg/kg
Reliability:	[2] Valid with restrictions A dose of 300 mg/kg was the highest dose tested in this subacute study.
Reference:	Derelanko, M.J., et al. Toxicity of Cyclohexanone Oxime: Hemotoxicity Following Subacute Exposure in Rats. Fundam. Appl. Toxicol. 5 : 117 – 127, 1985.

5.1.2 ACUTE INHALATION TOXICITY – No reliable information

5.1.3 ACUTE DERMAL TOXICITY

Type:	LD50; dermal absorption toxicity
Species:	New Zealand albino rabbits (5/sex/dose)
Value:	> 5000 mg/kg
Method:	Cyclohexanone oxime was applied to the shaved backs of rabbits for 24 hours at dose levels of 0 (distilled water), 0.8, 2 or 5 g/kg under an occluded patch and then observed for 14 days after dosing. Clinical signs and body weights were recorded. Blood samples were taken on days 1, 4 and 7 post-dosing and various hematological and chemical parameters were measured. Animals were terminated after 14 days, spleen weights were taken, and all rabbits were given gross autopsies.
Test substance:	cyclohexanone oxime (99.5% purity)
GLP:	Yes **[X]** No [ ] ? [ ]
Remarks:	No rabbits died at any dose level during the 24-hour dosing period or the 14-day post-dosing period. There were no adverse clinical signs, body weight or organ weight changes associated with treatment. However, reticulocyte counts were elevated on Day 1 in a dose-related manner in males; a similar but not statistically significant elevation occurred in females. Hemoglobin values were depressed in a dose-related manner in females; the depression was statistically significant only at the highest dose at 7 days after dosing. Methemoglobin levels were increased in both sexes in a dose-related manner at 4 days post-dosing, but not at either 1 or 7 days post-dosing. These results suggest that cyclohexanone oxime may be absorbed through the skin in toxicologically significant amounts.
Reliability:	**[2]** valid with restrictions No mortality occurred at the highest dose tested – 5000 mg/kg, an exceptionally high dose for an acute dermal absorption study.
Reference:	Gad, S.C., Derelanko, M.J., Powers, W.J., Mulder, S., Gavigan, F. and P.C.Babich. Toxicity of Cyclohexanone Oxime: Acute Dermal and Subchronic Oral Studies. Fundam. Appl. Toxicol. 5: 128-136, 1985.

5.1.4 ACUTE INTRAPERITONEAL TOXICITY

:	Type of Test:	LD50
	Species:	Male mice (strain unknown)
	Value:	250 mg/kg
	Method:	No information available
	Test Substance:	Cyclohexanone Oxime (unknown purity)
	GLP:	Yes [ ] No [X] ? [ ]

Remarks:	Limited information available; have not yet located full reference.
Reliability:	**[4]** Not assignable because limited study information was available
Reference:	Plzak, V. and J. Doull. National Technical information Services, No. AD-691490. US Department of Commerce, Washington, D.C., 1969.

5.4 REPEATED DOSE TOXICITY

A. Preferred Result

Type:	A 90-Day Oral Gavage Study in Rats
Species/strain:	Fischer 344 Male and Female rats (15/sex/exposure level)
Route of Administration:	Oral Gavage
Exposure period:	10 rats/sex/dose for 30 days 10 rats/sex/dose for 60 days 20 rats/sex/dose for 90 days
Frequency of treatment:	5 days/week
Post-dosing observation period:	None
Dose Levels:	0, 0.25, 2.5 and 25 mg/kg bw
Control group:	Yes (distilled water)
Method:	Groups of rats were dosed by oral gavage with cyclohexanol oxime for 5 days/week for 30 days (10 rats/sex/dose), 60 days (10 rats/sex/dose) or 90 days (20 rats/sex/dose) at doses of 0, 0.25, 2.5 or 25 mg/kg body weight. All rats were observed for adverse clinical signs daily and for neurobehavioral effects, body weight changes, and food consumption on a weekly basis. At dosing termination, hematology, blood chemistry and urinalysis measurements were conducted, as well as a complete histopathological examination of tissues.
Test Substance:	Cyclohexanone Oxime (>99.5% purity)
GLP;	Yes [X] No [ ] ? [ ]
Results:	There were no significant effects of cyclohenanone oxime on either body weight or food consumption; a slight mortality occurred at the highest dose (3 female rats) which may or may not have been treatment-related. In males, treatment-related effects occurred during the first 9 weeks of dosing and included red nasal discharge (highest dose only), chromodacryorrhea and swollen conjunctiva (high and mid

doses), and corneal opacity (all doses). These observations gradually subsided and disappeared by the end of the study. In females, there were no adverse clinical signs during the first 2 weeks of dosing. After that time, adverse signs included chromodacryorrhea (high dose) and corneal opacity (high and mid dose), both of which gradually subsided but never completely disappeared by study termination. Relative to haematology, after 90 days of dosing, there was a dose-related decrease in erythrocytes, hemoglobin and hematocrit, accompanied by an increase in circulating reticulocytes and nucleated erythrocytes, suggesting an increased erythropoeisis in the spleen and bone marrow. The latter changes were confirmed by gross autopsy (splenomegaly) and by histopathological examination. Other than histopathology in spleen and bone marrow, no other organs or tissues were adversely affected. Since the major hematological effects were no severe (no evidence of anemia, e.g.), recovery would be expected upon removal from exposure.

Conclusion: When rats were exposed repeatedly by oral gavage for up to 90 days, the primary effect of cyclohexanone oxime was increased destruction of erythrocytes with a compensatory increase in erythropoeisis without a noticeable anemia. The bone marrow was able to respond in a sufficient manner to keep up with the added needs. These effects were seen at all dose levels. Since these effects after 90 days of dosing were not severe, recovery would be expected.

Data Quality (Klimisch Code): [1] Valid without restrictions

Reference: Gad, S.C., Derelanko, M.J., Powers, W.J., Mulder, S., Gavigan, F. and P.C.Babich. Toxicity of Cyclohexanone Oxime: Acute Dermal and Subchronic Oral Studies. Fundam. Appl. Toxicol. 5: 128-136, 1985.

B. Supporting Results

Type; A 90-Day Drinking Water Study in Mice

Species/Strain: B6C3F1 Male and Female Mice

Route of Administration: Oral (via drinking water)

Frequency of Treatment: Daily

Dosing Period: 90 Days

Post-Dosing Observation Period: None

Dose Levels: 0, 625, 1250, 2500, 5000 and 10000 ppm cyclohexanone oxime in the drinking water

Control Group: Yes (water alone)

Method: Mice (10/sex/dose) were given drinking watrer containing 0, 625, 1250, 2500, 5000 and 10000 ppm cyclohexanone oxime daily for 90 days. Mice were observed twice daily for mortality and adverse

clinical signs. Clinical observations and body weights were recorded weekly and water consumption was recorded twice weekly. Complete gross and histopathological examinations were conducted at study termination. Sperm motility and vaginal cytology evaluations were performed on mice in the 0, 1250, 2500 and 5000 ppm dose groups. Males were evaluated for necropsy body weight and reproductive organ weights, and epididymal spermatozoal data. Females were evaluated for necropsy body weights, estrous cycle length, and the percent of cycle spent in the various stages.

Test Substance: Cyclohexanone Oxime (>99% purity)

GLP: Yes [X] No [ ] ? [ ]

Results: Deaths occurred in the 10000 ppm groups and weight gain was depressed in males and females given 10000 ppm and also in females given 5000 ppm. There were significant increased in the relative spleen weights at both 5000 and 10000 ppm, and in the relative liver weights of male and female mice dosed at 10000 ppm. Microscopically, hematopoeitic cell proliferation was seen in the spleens of males and females in both the 5000 and 10000 ppm groups. In the liver, centrilobular cell hypertrophy was seen in males at 2500, 5000 and 10000 ppm and in females at 5000 and 10000 ppm. Olfactory epithelial degeneration was seen in all dose groups. There were no significant differences in sperm motility of vaginal cytology parameters between dosed and control males and females.

Conclusion: The major targets of cyclohexanone oxime administered in the drinking water for 90 days to mice were the erythrocyte, spleen, liver and nasal epithelium. The NOEL for erythrotoxicity and hematopoeitic cell proliferation in the spleen was 2500 ppm. The NOEL for hepatotoxicity was 1250 ppm for males and 2500 for females following 13 weeks of dosing. Some nasal olfactory epithelial degeneration was observed at all dose levels; only at 625 ppm in males was the incidence of this lesion not significantly different from controls. There were no effects on sperm motility or vaginal cytology
parameters at doses as high as 5000 ppm (highest dose evaluated).

Data Quality
(Klimisch Code): [1] Valid without restrictions

Reference: Burka, L.T. NTP Technical Report on Toxicity Studies of Cyclohexanone Oxime. NTP Report Series No. 50, NIH Publication No. 96-3934, 1996.

5.5 GENETIC TOXICITY IN VITRO

A. Bacterial In Vitro Test

(1) Type: Bacterial reverse mutation assay

System of testing: Preincubation protocol

Concentration: cyclohexanone oxime concentrations ranged from 33 μg/plate to 3333 μg/plate (with metabolic activation) and from 333 to 6666 μg/plate (without metabolic activation); at least 5 doses tested

Method of Activation: With [ ]; Without [ ]; With and Without [X]; No data [ ]

Results: Not mutagenic in Salmonella typhimurium strains TA97, TA98, and TA100, with or without S9 activation. Positive evidence of mutagenicity only in strain TA1535 with hamster S9 activation but negative in same strain with rat liver S9 and negative without any S9 activation.

Test Substance: Cyclohexanone Oxime (>99% purity)

Cytotoxicity Concentration: >3333 μg/plate with S9 activation; >6666 μg/plate without S9 activation

Precipitation Concentration: No data

Method: Testing was performed as reported by Zeiger (Environ. Mol. Mutagen. 19 (Suppl. 21): 2-14, 1992). Cyclohexanone oxime was incubated with Salmonella typhimurium tester strains (TA97, TA98, TA100 and TA1535) either in buffer (without activation) or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rats or Syrian hamster liver) for 20 minutes at 37°C. Top agar supplemented with l-histidine and d-biotin was added and the contents of all tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37°C. Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least 5 doses of cyclohexanone oxime. All positive assays were repeated under the conditions that elicited a positive response; all negative assays were also repeated.

GLP: Yes [X] No [ ] ? [ ]

Reliability: [2] valid with restrictions
This oxime was positive in TA1535 but not in TA100, a more sensitive strain for the same kind of mutation.

Reference: Burka, L.T. NTP Technical Report on Toxicity Studies of Cyclohexanone Oxime. NTP Report Series No. 50, NIH Publication No. 96-3934, 1996.

(2) Type: Other Point Mutation Assays (Supporting Data)

Summary:

Under similar experimental conditions, Prival (2001) reproduced the preceding positive result in strain TA1535 using hamster liver S9, without evidence of mutagenicity in strain TA 100.

However, negative results with cyclohexanone oxime were obtained in mutagenicity tests with several strains of *Salmonella typhimurium*, with and without metabolic activation (Araki 1986; Rogers-Back 1988) and with Escherichia coli strain WP2 (Araki 1986). The only other mutagenic activity reported for cyclohexanol oxime was noted in L5178Y mouse lymphoma cells treated in the absence of S9 activation; the addition of rat liver S9 eliminated the mutagenic effect (Rogers-Back 1988).

References:

Araki, A., et al. Mutagenicity of Oxime Compounds in the S. typhimurium TA98, TA100, TA2637, and E. coli WP2 uvrA/pKM101. Mutat. Res. 164: 263, 1986.

Prival, M.J. Anomalous mutagenicity profile of cyclohexanone oxime in bacteria: cell survival in background lawns. Mutat. Res. 497: 1-9, 2001.

Rogers-Back, A.M. et al. Genotoxicity of 6 Oxime Compounds with Salmonella-Mammalian-Microsome Assay and Mouse Lymphoma TK Assay. Mutat. Res. 204: 149-162, 1988.

B. Non-Bacterial *In Vitro* Test

Type:	Cytogenetic assay (chromosome aberration)
System of testing:	Chinese hamster ovary (CHO) cells
Concentration:	Doses of cyclohenanone oxime ranging from 500 to 5000 μg/ml
Metabolic activation:	With [ ]; Without [ ]; With and Without [**X**]; No data [ ]
Results:	Negative
Cytotoxicity Concentration:	>>5000 μg/ml
Precipitation Concentration:	5000 μg/ml
Genotoxic effects:	None
Method:	Testing was performed as reported by Galloway (Environ. Mol. Mutagen. 10 (Suppl. 10): 1-175, 1987). Cyclohexanone oxime was tested in cultured CHO cells for induction of chromosome aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Each test consisted of concurrent solvent and positive controls and of at least 3 doses of cyclohexanone oxime. In the absence of toxicity, 5000 μg/ml was selected as the high dose. A single flask per dose was used; tests yielding equivocal or positive results were repeated. In the ABS test without S9, cells were incubated in McCoy's 5A medium with cyclohexanone oxime for 10 hours; Colcemid was added and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with cyclohexanone oxime and S9 for 2 hours, the treatment medium was removed, and the cells were then incubated for 10 hours in fresh medium. Colcemid was added for the final 2 hours. Cells were then harvested in the same manner as for

treatment without S9. For scoring, cells were selected on the basis of good morphology and completeness of karyotype(21±2 chromosomes) and all slides were scored blind. Two hundred first-division metaphase cells were scored at each dose level.

GLP: Yes [X] No [ ] ? [ ]

Test substance: Cyclohexanone Oxime (>99% purity)

Remarks: None

Reliability: [2] Valid with restrictions

Reference: Burka, L.T. NTP Technical Report on Toxicity Studies of Cyclohexanone Oxime. NTP Report Series No. 50, NIH Publication No. 96-3934, 1996.

5.6 GENETIC TOXICITY *IN VIVO*

(A) Type: Micronucleus Assay

Species/strain: B6C3F1 Mice

Sex: Female [ ]; Male [ ]; Male/Female [X]; No data [ ]

Route of Administration: Oral (drinking water); intraperitoneal injection

Dosing Period: 90 Days; over 3 days at 24-hour intervals ..... 1(

Doses: 0, 625, 1250, 2500, 5000, and 10000 ppm in the water;
400, 600, 800 and 1000 mg/kg (ip).

Results: Negative in 5 mice/sex dose (oral study) and in 5 male mice (ip study)

Effect on mitotic index or P/N ratio: No information

Genotoxic effects: Not an *in vivo* mutagen

Method: A detailed discussion of this micronucleus assay on peripheral blood has been presented by MacGregor (Fundam. Appl.Toxicol. 14: 513-522, 1990). At the end of a 90-day drinking water study on cyclohexanone oxime, peripheral blood samples were taken from 5 mice/sex/dose (highest dose in the drinking water was 10000 ppm), smears were immediately prepared and fixed in absolute methanol, and the slides were then stained with a chromatin-specific fluorescent dye and coded. Two thousand normochromatic erythrocytes were scored in each of 5 mice/sex in each of the 5 dose groups. The criteria of Schmid (In "Chemical Mutagens: Principles and Methods for their Detection", Vol. 4, A.Hollander (Ed.), pp. 31-53, Plenum Press, New York, 1976) were used in defining micronuclei.

For the intraperitoneal micronucleus test, after preliminary rangefinding, 5 male mice/dose were injected (ip) over 3 days at 24-hour intervals with cyclohexanone oxime dissolved in corn oil (total dose volume of 0.4 ml) at doses of 0, 400, 600, 800 and 1000 mg/kg bw. Solvent control animals received 0.4 ml of corn oil only and positive control mice got injections of cyclophosphamide. Twenty-four hours after the third injection, the mice were sacrificed and smears of the bone marrow cells (from the femur) were prepared. Air-dried smears were fixed and stained; 2000 polychromatic erythrocytes were scored for frequency of micronucleated cells in each of 5 mice at each of 4 doses.

GLP: Yes [X] No [ ] ? [ ]

Test substance: Cyclohexanone Oxime (>99% purity)

Remarks: In micronucleus tests conducted in mice by two different routes of administration (oral and ip), cyclohexanone oxime showed no evidence of *in vivo* mutagenicity.

Reliability: [1] Valid without restrictions

Reference: Burka, L.T. NTP Technical Report on Toxicity Studies of Cyclohexanone Oxime. NTP Report Series No. 50, NIH Publication No. 96-3934, 1996

(B) Type: Gene Mutation *In Vivo* (Supporting Data)

Summary: When male fruit flies (*Drosophila melanogaster*) were administered cyclohexanone oxime (8.8 mM) by feeding, there was no increase in the frequency of sex-linked recessive mutations in germ cells.

Reference: Vogel, E. and J.L.R. Chandler. Mutagenicity Testing of Cyclamate and Some Pesticides in *Drosophila Melanogaster*. Experientia 30: 621-623, 1974.

5.7 TOXICITY TO REPRODUCTION – No data available

5.8 DEVELOPMENTAL TOXICITY: No data available

5.11 EXPERIENCE WITH HUMAN EXPOSURE (WORKPLACE)

No definitive studies on human exposure to cyclohexanone oxime were found. No occupational exposure limits(OSHA PEL or ACGIH TLV® have been established. In one older reference(Finkel, A.J. in Hamilton and Hardy's Industrial Toxicology, 4th Edition, John Wright PSG, Boston, MA, 1983), hematological disorders were reported in humans exposed to cyclohexanone oxime. It was also stated that dermatitis

and skin sensitization may also be potential effects of occupational exposure. No other details were given.

6.0 REFERENCES